MEMORANDUM

To: File

From: Jason Woo, MD, MPH, FACOG
Associate Director, Medical Affairs

Through: Michael Levy, Director, Division of New Drugs and Labeling Compliance

Jennifer Devine, Acting Assistant Director, Division of New Drugs and Labeling Compliance

Date: June 5, 2008

Subject: Literature Search – Studies of Hydrocodone Drug Products for Antitussive Indications

On October 1, 2007, the Food and Drug Administration ("FDA") published a notice in the *Federal Register* announcing its "intention to take enforcement action . . . against unapproved drug products containing hydrocodone bitartrate, or any other salt or ester of hydrocodone . . . , and persons who manufacture or cause the manufacture of such products or their shipment in interstate commerce." 72 Fed. Reg. 55780, 55780-81 (October 1, 2007) ("*2007 Notice*"). I was asked to consider whether there is published literature reflecting adequate and well-controlled studies that support a finding that drug products containing hydrocodone bitartrate are generally recognized as safe and effective (GRAS/E) for use as an antitussive (cough suppressant).[1] Based on my search and review of the literature, it is my assessment that there are not adequate and well-controlled studies sufficient to support a GRAS/E finding, and that such products are not GRAS/E.

[1] I am presently Associate Director for Medical and Scientific Affairs in the Office of Compliance, Center for Drug Evaluation and Research (CDER), FDA. I received a Master of Public Health from the University of Arizona in 2001, received my medical degree from the Uniformed Services University of the Health Sciences in 1992. I am board certified in obstetrics and gynecology, and licensed to practice medicine in Arizona and the District of Columbia. My qualifications are set forth in my curriculum vitae, which is attached. By virtue of my training and professional experience, I am familiar with the quantity and quality of evidence that is needed to establish the safety and effectiveness of drugs, criteria for adequate and well-controlled clinical investigations, and also with the standards for evaluating whether a drug is "generally recognized . . . as safe and effective" by qualified experts for its intended uses as set forth in under the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 321(p).

A. Background: The GRAS/E Standard

In order to be GRAS/E within the meaning of 21 U.S.C. § 321(p)(1), a drug must satisfy three criteria. *First*, the particular drug product at issue must have been subjected to adequate and well-controlled clinical investigations which establish that the product is safe and effective. *Second*, those investigations must have been published in the scientific literature so that they are available to qualified experts. *Third*, experts must generally agree, based on those published studies, that the product is safe and effective for its intended uses. A product's general recognition as GRAS/E must be evidenced by at least the same quality and quantity of data as are necessary to support approval of an NDA. I am also familiar with FDA's regulation at 21 C.F.R. § 314.126, which describes the characteristics of adequate and well-controlled clinical investigations. This regulation expresses many of the scientific principles underlying adequate and well-controlled clinical investigations. For a study to be adequate and well-controlled, it must, for example: enroll a sufficiently large number of adequately characterized study participants; have at least one control group; minimize bias, usually through random assignments of study participants to control and treatment groups and through the blinding of participants and investigators to those assignments; and analyze the results of the study adequately to assess the effects of the treatment. The purpose of requiring such rigorously controlled investigations is to ensure that patients receive only those drugs whose safety and effectiveness have been established by accepted scientific methods.

Assessing whether there is adequate clinical literature to support a determination of GRAS/E starts with searches of established medical literature databases (e.g., PubMed, Medline) for keywords, beginning with the drug ingredient and including additional terms to limit search results to articles/studies involving the indication and dosage form under consideration. When available, product brand name and manufacturer name could be searched to help ensure that any published studies identified relate to the specific drug product at issue. Additionally, searching by specific types of studies, i.e. randomized and/or controlled, would specify the type and quality of the information that would be expected to be available to support a GRAS/E determination. Review of abstracts of studies meeting these search criteria would provide an overview of clinical literature that might support a GRAS/E determination. Additional review of the abstracts could be expected to eliminate studies that would not support a GRAS/E determination for a drug product of a specific dosage form and strength, and for the particular indication at issue. Further, more detailed, review of the full text of the article(s) to assess their relevance to a GRAS/E determination generally would be necessary only if the search criteria and review of the abstracts identify studies having the fundamental requirements for adequate and well-controlled studies. Literature searches that do not identify at least 2 adequate and well-controlled studies would likely exclude the possibility of a determination of GRAS/E status for any given drug product.

B. Literature Search and Review

On March 27, 2008, I conducted several searches for articles referring to hydrocodone. I performed internet-based electronic searches on both MEDLINE and PubMed, which are databases provided by the U.S. National Library of Medicine (NLM). PubMed "includes over 17 million citations from MEDLINE and other life science journals for biomedical articles back to the 1950s." [2] MEDLINE is a "bibliographic database that contains references to journal articles in the life sciences with a concentration on biomedicine."[3] MEDLINE also contains citations from 1950 to the present, and may contain some older material.[4]

I conducted searches in each database, and also used a variety of search terms, some of which were very broad ("hydrocodone"), and others more refined to focus on articles that, for example, refer to both "hydrocodone" and "cough," or to "hydrocodone" and "clinical trial."

The searches in PubMed and MEDLINE generally produced the same relevant studies. The searches identified only one study involving the use of an oral dose of hydrocodone as an antitussive. This study, however, was specific to use by cancer patients and was also a "phase 2" study (i.e., was conducted in a relatively small number of patients to gather preliminary evidence of effectiveness and not designed to fully evaluate the overall benefit-risk relationship of the drug or to provide an adequate basis for labeling).[5] The abstract for this study follows:

> PURPOSE: Cough is a common symptom in advanced cancer. The use of hydrocodone as an antitussive has not been studied previously in this setting. This study evaluates hydrocodone for cough in advanced cancer METHODS: The results presented are from a phase II study with dose titration. Setting: Palliative medicine program in a tertiary referral center PATIENTS: 25 consecutive patients with cough from irreversible causes, on a stable opioid regimen for the prior 24 hours, and no previous or current use of hydrocodone for cough. INTERVENTION: 5 mg hydrocodone was administered twice daily. The dose was then titrated daily (maximum: 60 mg/24 h), if needed, until a > or = 50 percent improvement of the frequency of cough was achieved and then maintained for three consecutive days. MEASUREMENTS: Cough severity, frequency, complications, and hydrocodone side effects. RESULTS: 20 persons (10 women and 10 men) completed study evaluation. Median age was 63 years (range: 42-82). Nine patients had lung cancer and seven had lung or pleura metastases; 19 patients had at least 50 percent improvement of their cough frequency. The median best response was 70 percent improvement in the cough frequency (range: 50-90 percent). Median hydrocodone dose associated with the

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[2] www.ncbi.nlm.nih.gov/entrez/query/static/overview.html#Introduction

[3] *Id.*

[4] Any search of an electronic database is limited by the searchable terms that are attached to each article in the database. However, both PubMed and Medline are recognized as the primary databases for searchable terms in the clinical literature. The alternative approach of searching based on the references cited in known articles or books, while possibly capturing different opinions, summaries, or case studies, would not likely identify additional literature (not already identified by PubMed or Medline searches) reflecting the kind of controlled clinical trial data needed to support a GRAS/E determination.

[5] Homsi J; Walsh D; Nelson KA; et al. A phase II study of hydrocodone for cough in advanced cancer. **Am J Hosp Palliat Care.** 2002; 19(1):49-56.

best response was 10 mg/day (range: 5-30 mg/day). Cough severity, frequency, associated symptoms and complications, and activities of daily living improved significantly. Side effects of hydrocodone (dry mouth, nausea, and drowsiness) were tolerable and rated as mild. CONCLUSIONS: Hydrocodone is effective and safe to treat cough in advanced cancer. A starting dose of 10 mg per day in divided doses seems effective. Dose escalation may be required. Most improved within one day.

This study was designed primarily to identify the appropriate range of dosing that would demonstrate effectiveness and minimize side effects in an opioid-stable population. In this population, the use of other opioids for pain management associated with cancer treatment and physiologic tolerance of opioids limits or precludes the applicability of the study's conclusion to a general population that does not routinely have exposure to other opioids or an underlying cancer condition affecting their tolerance to hydrocodone. In addition, the study was neither blinded nor controlled.

I identified two randomized, controlled trials (RCT); they are not relevant because they involved the intravenous administration of hydrocodone to suppress cough in patients undergoing a flexible bronchoscopy procedure, rather than for symptomatic relief of cough.[6] In addition, the study findings related to the symptomatic relief of cough are a secondary outcome that is confounded, or confused, by the primary outcome of interest, which was to suppress the cough reflex during the procedure. When the positive effect of hydrocodone allowed the surgeon to perform the procedure more easily, that likely resulted in less physical trauma to the patients, which would also reduce the patients' cough symptoms. Thus, the extent to which the symptomatic relief of cough can be attributed to the direct effect of hydrocodone, versus reduced trauma, is uncertain.

My review also identified one characterization study, which describes the range of experience – psychomotor, physiological, and subjective (e.g., "liking" score) – with the drug over time by 18 non-drug-abusing individuals.[7] This type of study is useful in prompting questions that merit further study, especially as it relates to the safety of the drug, but is not a study from which one can draw conclusions about the safety or efficacy of the drug in any population of users. This type of study would typically be part of the "phase 2" information that is generated prior to a more thorough and detailed controlled clinical trial.

I also identified four summary (opinion) articles[8] that did not provide any additional clinical trial information that would be relevant to evaluating the safety and efficacy of using

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[6] Stolz D, Chhajed PN, Leuppi J, Pfimlin, E, Tam, M Nebulized lidocaine for flexible bronchoscopy: a randomized, double-blind, placebo-controlled trial. **Chest.** 2005 Sep; 128(3):1756-60; Stolz D, Chhajed PN, Leuppi JD, Brutsche M, Pfimlin E, Tamm M Cough suppression during flexible bronchoscopy using combined sedation with midazolam and hydrocodone: a randomised, double-blind, placebo-controlled trial. **Thorax.** 2004 Sep;59(9):773-6.

[7] Characterizing the subjective, psychomotor, and physiological effects of a hydrocodone combination product (Hycodan) in non-drug-abusing volunteers. **Psychopharmacology (Berl).** 2003 Jan;165(2):146-56.

[8] Simasek M, Blandino DA Treatment of the common cold. **Am Fam Physician.** 2007 Feb 15;75(4):515-20; Estafan B, LeGrand S, Management of cough in advanced cancer. **J Support Oncol.** 2004 Nov-Dec; 2(6):523-7; Homsi J, Walsh D, Nelson KA, LeGrand SB, Davis M Hydrocodone for cough in advanced cancer. **Am J Hosp**

hydrocodone for an antitussive indication. The other articles resulting from my searches involved the use of hydrocodone for pain/analgesic indications, animal studies, or other issues relating to hydrocodone such as toxicity, dependence, or abuse, and scientific techniques to identify the drug.

Below is a chart that briefly summarizes the searches I conducted, including the databases I searched, the specific search term(s) I used, the number of results from each search, and thumbnail summary of the extent to which the results were relevant to the inquiry.

PubMed Searches: 3/27/08

Search Terms	Number of Articles	Types of Relevant Articles/Studies
Hydrocodone	338	Broad, mostly for pain indication
Hydrocodone, English	323	As above, limited to articles in English only
Hydrocodone, English Clinical Trial	78	1 Phase 2 study 2 RCT re: intravenous (IV) administration during FB procedure 1 characterization study Most related to pain indication
Hydrocodone, English Randomized Controlled Trials	64	2 RCT re: IV admin. (repeat - same studies as noted above) 1 characterization study (repeat) Most related to pain indication
Hydrocodone, English, NIH Controlled Clinical Trial	6	None relevant
Hydrocodone, Cough	14	1 RCT re: IV admin. (repeat) 4 summary articles

Palliat Care. 2000 Sep-Oct;17(5):342-6; Homsi J, Walsh D, Nelson KA Important drugs for cough in advanced cancer. **Support Care Center.** 2001 Nov;9(8):565-74.

MEDLINE Searches

Search Terms	Articles found	Types of Relevant Articles/Studies
Hydrocodone	312	1 Phase 2 (repeat) 2 RCTs re: IV admin (repeat) 4 summary articles (repeat) Most related to pain indication
Hydrocodone, Antitussive	19	1 Phase 2 (repeat) 1 RCT re: IV admin. (repeat) 4 summary articles (repeat)
Hydrocodone, Cough	16	1 Phase 2 (repeat) 2 RCTs re: IV admin (repeat) 4 summary articles (repeat)

C. Conclusion

It is my judgment that the published literature described above does not include any adequate and well-controlled investigations or any other scientific literature sufficiently demonstrating the safety and effectiveness of hydrocodone drug products in any strength or dosage form for an antitussive indication. While a more limited review would have quickly revealed the lack of adequate controlled clinical trials in the published literature sufficient to support a GRAS/E determination for the use of hydrocodone in the treatment of cough, my more intensive and thorough review of these abstracts, articles, and additional citations shows that the available data are limited to the type of information that typically would be generated during the development of a drug's safety and efficacy profile (i.e., during phase 2 development). Based on the results of the above-described literature searches and review of articles, and on my training and professional experience in the evaluation of safety and effectiveness of drugs, I do not believe that hydrocodone drug products are generally recognized as safe and effective among qualified experts for antitussive indications.